PATENT SPECIFICATION (11) 1323 161

1323 161

DRAWINGS ATTACHED

(21) Application No. 7255/70 (22) Filed 16 Feb. 1970

(61) Patent of Addition to No. 1 226 555 dated 24 July 1968

(23) Complete Specification filed 19 April 1971

(44) Complete Specification published 11 July 1973

(51) International Classification A61K 9/00, 21/00

(52) Index at acceptance
A5B 732 736 73Y 751 753 754 759 75Y 764

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(54) PENICILLIN COMPOSITION

(71) We, JOHN WYETH & BROTHER LIMITED, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, a British Company, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a suspension formulation of acetoxymethyl benzylpenicillinate (penamecillin) and to a method for its preparation. Penamecillin is the subject of British Patent No. 1,003,479. This application is for a further development of the invention of our U.K. Patent No. 1,226,555 to which this application is for a Patent-of-Addition.

Penamecillin has an extremely bitter taste and it is also moisture sensitive. For these reasons it is extremely difficult to find a stable liquid suspension formulation for oral use in which the bitter taste is masked, especially for administration to children, and efforts have been directed to the preparation of a powder form of penamecillin which can be formulated into a form which is capable of being constituted ("reconstituted") into an aqueous liquid suspension before use, which is of adequate stability for the desired period and in which the bitter taste is alleviated or overcome. The invention provides such a powder form of penamecillin utilising a carefully formulated coating wax and by the use of a spray-congealing process under carefully controlled conditions.

Accordingly, the invention provides a process for the preparation of a coated powder of acetoxymethyl benzylpenicillinate in which acetoxymethyl benzylpenicillinate is finely comminuted to a particle size below 10μ and then preferably by using a high speed mixer with a high shear mixing head e.g. using a Silverson mixer, is intimately mixed with and suspended in a molten non-toxic coating wax mixture having a melting point not greater than 95°C comprising a mixture of at least 50% by weight of hydrogenated castor oil (castor wax) and up to 50% by weight of a fatty acid having at least 16 carbon atoms in the molecule or mixture of such fatty acids or wax based thereon, the amount of acetoxymethyl benzylpenicillinate not exceeding 22.5% by weight of the total mixture, at a temperature of 75—95°C, preferably 80—90°C, is atomised to form a fine spray and is spray-congealed. As a result of spray-congealing the powder has a coated particle size such that the particles pass an A.S.T.M. 100 mesh sieve.

The invention also provides a powder of finely comminuted acetoxymethyl benzylpenicillinate of particle size below 10μ, coated with a non-toxic coating wax having a melting point not greater than 95°C, comprising a mixture of at least 50% by weight of hydrogenated castor oil and up to 50% by weight of a fatty acid having at least 16 carbon atoms in the molecule or mixture of such fatty acids or wax based thereon, the amount of acetoxymethyl benzylpenicillinate not exceeding 22.5% by weight of the total mixture, by a spray-congealing process.

For the coating wax a mixture of hydrogenated castor oil and a "stearic acid" containing a substantially 50:50 by weight mixture of stearic acid and palmitic acid is particularly preferred. Palmitic acid, behenic acid and other higher fatty acids and beeswax can also be used. "Stearic acid" without the hydrogenated castor oil gave a free flowing product with an initially bland taste but rapidly developed a bitter after-taste.

Preferably the amount of penamecillin in the wax mixture does not exceed 20% by weight so that adequate taste masking is obtained. Above 22.5% the bitter taste of penamecillin is no longer adequately masked; moreover a mixture containing 20% of penamecillin is preferred to render the suspension sufficiently fluid to flow through the atomiser used at 75°C. It is also preferred to use a mixture of the fatty acid or wax and hydrogenated castor oil containing 33% or more by weight of the fatty acid or wax since an increased proportion

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of the fatty acid or wax allows easier handling of the molten wax slurry during the spray-congealing process.

During spray-congealing the flow-rate is preferably as fast as consistent with avoiding flooding of the feed unit. In this way the powder formed gives a less gritty suspension.

The coated powder is ultimately formulated with conventional excipients, preferably with other suspension constituents, so that by shaking with water, a suspension suitable for oral administration is obtained. For this purpose other constituents (excipients) such as sugars, buffering agents e.g. sodium citrate and citric acid, methyl celluloses as suspending agents and wetting agents, saccharin, and other materials used in making oral suspensions such as dyes and other sweetening agents can be used. The constituted suspension preferably is buffered to pH 6.5 as this gives maximum stability.

A method of spray-congealing in accordance with the invention is now described with reference to the drawings accompanying the provisional specification in which Figure 1 shows the head of a spray-congealing apparatus in conjunction with a pumping unit, used for the laboratory scale operation of the process described in the Examples herein, and Figure 2 shows the whole apparatus on a smaller scale.

In figure 1 a stainless steel reservoir 1 surrounded by electric heating tape 3 is provided with a mixer 2. The base of the reservoir is fitted with a gear pump 4 (only one gear shown) driven by a motor 8 through a 4:1 reduction drive 5, shafting 7 and coupling 6. The gear pump 4 supplies molten wax by a U-shaped copper connecting tube 9 to a polytetrafluoroethylene tube 10 surrounded by an outer glass tube 11 fitted with a B19 socket 12, a B19/B24 expansion adaptor 13 and a borosilicate glass funnel 14 fitted with a B24 joint. The glass tube and funnel assembly is surrounded by an electric heating tape 15 and electric heating mantle 16. The funnel has an outlet 17 at its top. The tube 10 feeds molten wax to a Niro atomiser 18 comprising a compressed air motor 19 driving an atomiser wheel 20. The feed tube 21 and foot of atomiser are provided with electric heating cords 22. A compressed air supply 24 drives the motor 19 and air is allowed to escape from the head of the atomiser unit. The atomiser is fitted into the internal well in the lid of a Niro Minor portable spray drying unit 25 fitted with a swirl generating air supply head 26.

In operation the waxes are combined and melted together in a heated container with gentle stirring, care being taken to ensure that the waxes are not heated above 100°C to avoid burning the waxes and thereby imparting an acrid taste. Penamecillin finely comminuted or micronised to a particle size not above 10μ (preferred average 3.5—4μ) is added part by part and the whole is homogenised by rapid stirring using a Silverson high speed mixer using the high speed to obtain a high rate of shear, and also maintaining the temperature of the suspension at 80°C. The suspension is then placed in the reservoir 1, stirred slowly and when the temperatures throughout the apparatus are steady, the suspension is then pumped via gear pump 4 and partly allowed to fall by gravity to the atomiser at a rate of >30g. per minute. The stirring is continued in reservoir 1 to maintain the suspension. Electrical heating is maintained by the tapes, cords and mantle 15, 16 and 22 to keep the wax at 80°C. Dry air (6 Kg/cm^2 pressure) is used to drive the atomiser motor 19 and air at room temperature is supplied (at 26) to the drying unit 25. This air could be cooled by dry ice or heated electrically but in general air at 20°C is suitable. A cloud of congealing wax/penamecillin droplets is driven onto the sides of the Niro dryer, falls to the bottom and is collected by a cyclone separator shown in Figure 2. The vortex created during spraying operations by the centrally positioned air inlet 26 helps to prevent the waxy particles from adhering to the walls of the chamber.

In order to start up, the Niro atomiser is placed in position in the well of the Niro dryer. The atomiser wheel is removed and brought to 50°C in an air oven. The homogenised mixture of penamecillin and waxes is placed in the reservoir 1 and the electric heaters are adjusted to maintain a wax temperature of 80°C throughout the pump, feed line and atomiser. The apparatus is left for about half an hour for the temperature to become steady and the atomiser wheel 20 is fitted to the spindle at the bottom of the atomiser, and mixer 2 is switched on. The dryer fan and atomiser wheel are switched on and the gear pump 4 is operated by switching on motor 8. After a sufficient amount of product has been collected the air, heaters and pumps are turned off. The product is removed, weighed and stored in glass jars and the remaining wax slurry is pumped from the reservoir 1 into a collecting receptacle and weighed.

The following examples illustrate the preparation of the coated powder in accordance with the invention, the preparation of a formulation suitable for reconstitution as an aqueous slurry for oral use, and some blood level tests on dogs showing the pharmacological properties of the products obtained. Percentages and parts are by weight.

Example 1

Hydrogenated Castor oil	65%)	
	)	4 parts
Yellow Beeswax	35%)	
Micronised penamecillin		1 part

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Example 2

Hydrogenated Castor oil	75%)	4 parts
Stearic acid (fine powder)	25%)	
Micronised penamecillin		1 part

Example 3

Hydrogenated Castor oil	65%)	4 parts
Stearic acid (fine powder)	35%)	
Micronised penamecillin		1 part

The product of Example 1 gave a very bland tasting aqueous suspension but the cost of beeswax is about 6% per batch greater than using stearic acid as in Example 3. Moreover the material of Example 3 gave better blood levels. The product of Example 3 had better handling properties in the molten stage than that of Example 2.

The grade of stearic acid used affects somewhat the taste masking properties of the wax coating. Thus Pristerine 65 stearic acid fine powder code 76702 [supplied by Prices' (Bromborough) Ltd.,] was better than Distec A121/P stearic acid. The differences arise from the fact that these stearic acids are mixtures containing differing proportions of constituents [Pristerine 65 contains 1% myristic acid, 52% palmitic acid, 43% stearic acid and 4% oleic acid: Distec A121/P contains 4% myristic acid, 25—35% palmitic acid and 60—70% stearic acid].

It is noted that a 50:50 stearic/palmitic acid mixture forms a low shrinking eutectic on congealing which may account for the better performance of Pristerine 65.

Example 4

Hydrogenated Castor oil	65%)	4 parts
Palmitic acid	35%)	
Penamecillin (micronised)		1 part

The product of Example 4 was similar to that of Example 3. When myristic acid (14 carbon atoms) was substituted for palmitic acid the product gave a bitter tasting suspension.

Example 5

Hydrogenated castor oil	60%)	4 parts
Stearic acid (fine powder)	40%)	
Micronised penamecillin		1 part

It was noted that if the penamecillin was not micronised blocking of the equipment tends to take place and the product has a poor taste.

The following conditions were found optimum for spray congealing powders according to Examples 1—4 using the Niro Minor portable spray drier:

Gear pump rate:	75 g. per minute
Atomiser pressure	90 p.s.i.
Atomiser air temperature about	50°C.
Circulating air temperature in the drier about 22°C but not above 25°C	
Reservoir temperature:	80°C
Channel temperature:	80°C±2°C
Butterfly valve:	maximum open

Example 6

Formulations of a powder for reconstitution as an aqueous oral suspension.

Coated penamecillin (Example 3)	17.5 %
Sucrose, granulated	20.0 %
Sodium citrate, anhydrous	2.0 %
Citric acid, anhydrous	0.01 %
*Methocel, methyl cellulose 15 cps.	4.00 %
*Methocel, methyl cellulose 400 cps.	1.00 %
Saccharin sodium	0.03 %
Water	to 100% (*ca* 60 ml.)

*Methocel is a Registered Trade Mark.

The following properties were found:

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Example	Type of Coating	Palatability
Control	Stearic acid	Breaks down in water within 15 minutes (observed microscopically). Bitter taste within 10 seconds in the mouth.
1	beeswax 35% castorwax 65%	Negligible breakdown after 14 days in water. No bitter taste after 150 seconds in mouth. Sweet honey taste.
3	stearic acid 35% castorwax 60%	Negligible breakdown after 14 days in water. No bitter taste after 150 seconds in mouth.
5	stearic acid 40% castorwax 60%	Negligible breakdown within 10 days in water. No bitter taste after 150 seconds in mouth.

Blood level studies were carried out using dogs dosed orally with a single oral dose of 25 mg/kg of the powder. After intervals of time given in Table 1 a sample of the dogs' blood was taken and the serum submitted to bioassay. The blood level results are given in Table 1.

TABLE 1

Time in hours	Finely comminuted penamecillin (control) in µg/ml	Stearic acid coated penamecillin (control) in µg/ml	Example 1 beeswax/ castorwax coated in µg/ml	Example 2 stearic acid/ castorwax coated in µg/ml	Product of Example 3 formulated for suspension in µg/ml
1	5.02	4.59	0.92	2.12	2.00
2	2.68	3.22	0.95	2.13	2.13
4	0.44	0.540	0.35	0.73	0.86
6	0.15	0.07	0.12	0.34	0.18
8	0.06	0.01	0.03	0.13	0.05
10	0.03	0.01	0.015	0.05	0.014
12	0.013	<0.01	<0.01	0.03	<0.01
No. of dogs	12	12	12	12	6

The stabilities of the powders are given in Table 2.

BNSDOCID: <GB_____1323161A_I_>

TABLE 2

Storage Time	% Penamecillin			
	Product of Example 1		Product of Example 3	
	25°C	37°C	25°C	37°C
Initial	19.2	19.2	19.6	19.6
2 Weeks	19.25	18.4	18.4	18.0
1 Month	—	19.9	19.6	19.0
2 Months	20.3	16.8	19.5	17.3
3 Months	18.55	17.5	18.1	11.0

The stabilities of two duplicate samples of the reconstituted suspension formulation of Example 6 are given in Table 3.

TABLE 3

	Sample *A* (theoretical concentration 175 mg/ml.)	Sample *B*
Initial Assay after reconstitution	142.2 mg/5 ml.	143.4 mg/5 ml.
After 5 days	146.0 mg/5 ml.	143.0 mg/5 ml.

WHAT WE CLAIM IS:—

1. A process for the preparation of a coated powder of acetoxymethyl benzylpenicillinate in which acetoxymethyl benzylpenicillinate is finely comminuted to a particle size below 10μ, is intimately mixed with and suspended in a molten non-toxic coating wax mixture having a melting point not greater than 95°C comprising a mixture of at least 50% by weight of hydrogenated castor oil and up to 50% by weight of a fatty acid having at least 16 carbon atoms in the molecule or a mixture of such fatty acids or wax based thereon, the amount of acetoxymethyl benzylpenicillinate not exceeding 22.5% by weight of the total mixture, at a temperature of 75—95°C, and the suspension, maintained at 75—95°C is atomised to form a fine spray and is spray congealed.

2. A process according to Claim 1 in which the intimate mixing is carried out with a high speed mixer having a high shear mixing head.

3. A process according to Claim 1 or Claim 2 in which the temperature used is 80—90°C.

4. A process according to any preceding claim in which the amount of acetoxymethyl benzylpenicillinate does not exceed 20% by weight of the total mixture.

5. A process according to any preceding claim in which the amount of the fatty acid component of the wax mixture is in the range 33 to 50% by weight.

6. A process according to any preceding claim in which in the spray congealing step the flow rate is as fast as consistent with avoiding flooding of the feed unit.

7. A process according to any preceding claim in which the fatty acid component of the wax mixture is a substantially 50:50 by weight stearic acid — palmitic acid mixture.

8. A process substantially as described herein and shown with reference to the drawings accompanying the provisional specification and any one of Examples 1 to 5.

9. A coated powder of acetoxymethyl benzylpenicillinate comprising finely comminuted acetoxymethyl benzylpenicillinate having a particle size below 10μ, coated by a spray-congealing process with a non-toxic coating wax having a melting point not greater than 95°C comprising a mixture of at least 50% by weight of hydrogenated castor oil and up to 50% by weight of a fatty acid having at least 16 carbon atoms in the molecule or a mixture of such fatty acids or wax based thereon, the amount of acetoxymethyl benzylpenicillinate not exceeding 22.5% by weight of the total mixture.

10. A coated powder according to Claim 9

BNSDOCID: <GB_____1323161A__I_>

in which the amount of acetoxymethyl benzylpenicillinate does not exceed 20% by weight of the total mixture.

11. A coated powder according to Claim 9 or Claim 10 in which the amount of fatty acid in the mixture is in the range 33—50% by weight.

12. A coated powder according to any one of Claims 9 to 11 in which the fatty acid component of the wax mixture is a substantially 50:50 by weight stearic-palmitic acid mixture.

13. A coated powder of acetoxymethyl benzylpenicillinate substantially as described herein and shown with reference to any one of Examples 1 to 5.

14. A powder for reconstitution by shaking with water to give a suspension suitable for oral administration comprising a coated powder according to any one of Claims 9 to 13 and conventional excipients.

15. A powder for reconstitution according to Claim 14 buffered so that when shaken with water a pH of 6.5 is given.

16. A powder for reconstitution substantially as described herein and shown with reference to Example 6.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1973.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

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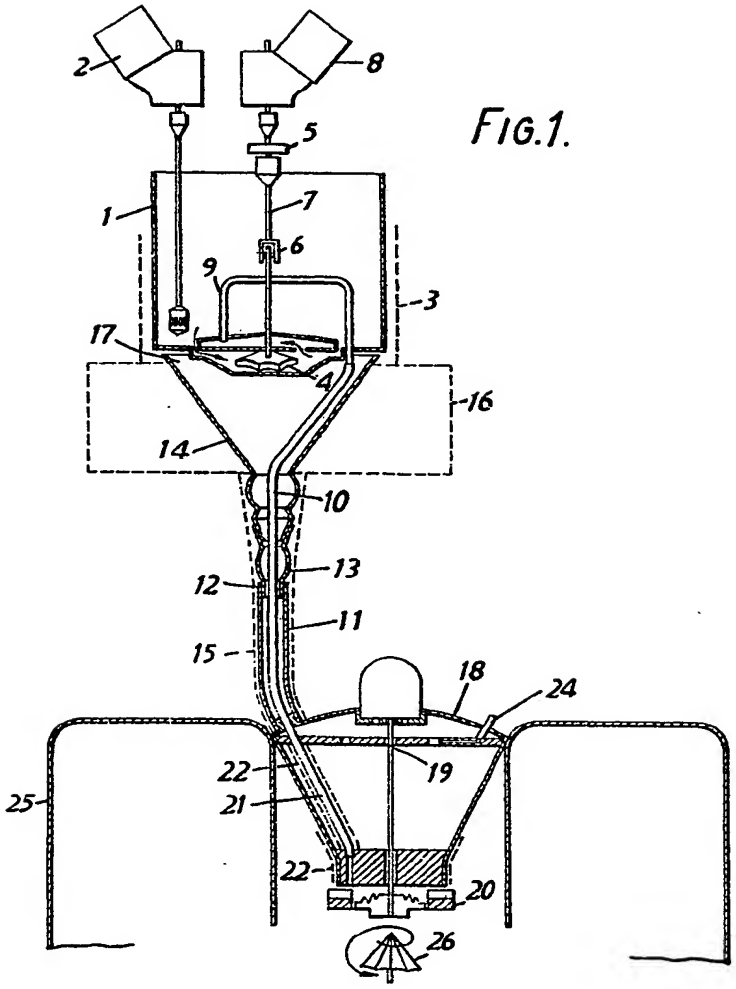

FIG.1.

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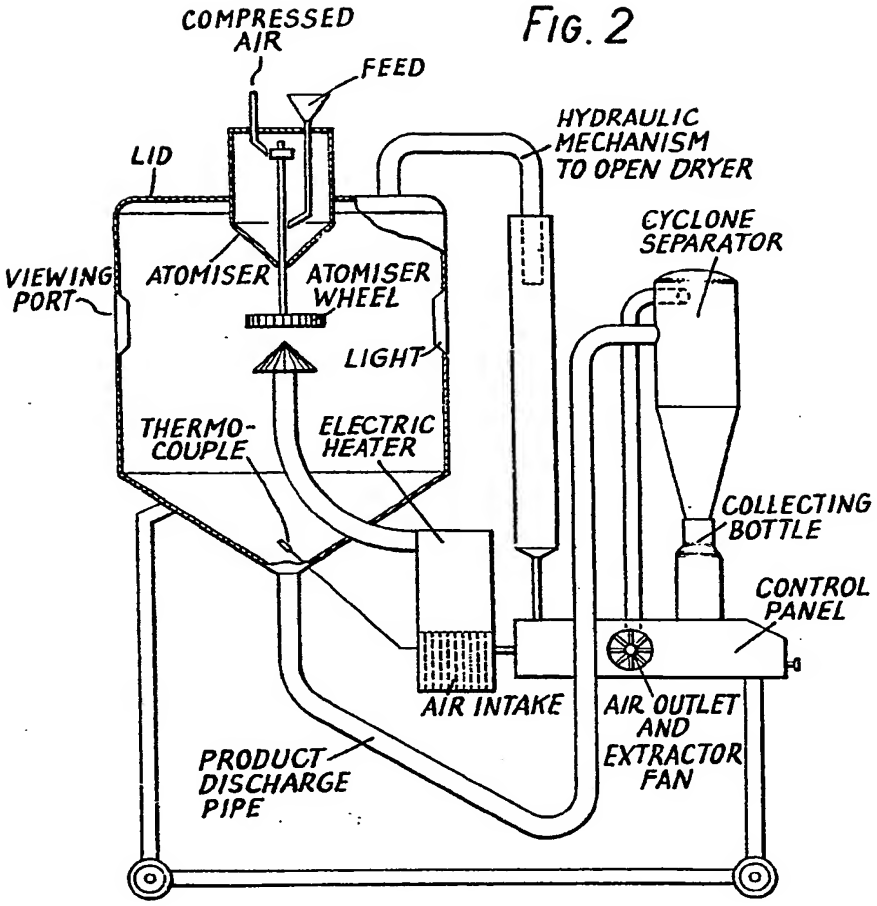
FIG. 2



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